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FORM PTO-1390  
(REV. 5-91)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

526 Rec'd PCT/PTO 04 JAN 2001

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 1<sup>st</sup> CFR 1.5)  
09/743206

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/GB99/02127

02 July 1999

04 July 1998

TITLE OF INVENTION

NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES

APPLICANT(S) FOR DO/EO/US

PARKER, Dawood; HARRISON, David Keith

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 19(1)
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau)
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau)
  - b. ☒ have been transmitted by the International Bureau. (Art. 19 Amendments in IPEA Report)
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3))
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: International Search Report by European Patent Office  
International Preliminary Examination Report  
"Express Mail" mailing label number EE 310251681 US  
Date of Deposit January 4, 2001

I hereby certify that this paper is being deposited with the U.S. Postal Service "Express Mail-Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to: Hon. Commissioner of Patents and Trademarks, Washington, D. C. 20231.

*Edwin D. Schindler*

Edwin D. Schindler, Reg. No. 31,459

January 4, 2001

Date

09/743206

17. ☒ The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)): \$860.00  
 Search Report has been prepared by the EPO or JPO..... ~~\$830.00~~

International preliminary examination fee paid to USPTO (37 CFR 1.482)  
 ..... \$640.00

No international preliminary examination fee paid to USPTO (37 CFR 1.482)  
 but international search fee paid to USPTO (37 CFR 1.445(a)(2)).. \$710.00

Neither international preliminary examination fee (37 CFR 1.482) nor  
 international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... \$950.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)  
 and all claims satisfied provisions of PCT Article 33(2)-(4)..... \$90.00

ENTER APPROPRIATE BASIC FEE AMOUNT = \$ 860.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30  
 months from the earliest claimed priority date (37 CFR 1.492(e)). \$ -0-

Claims	Number Filed	Number Extra	Rate	
Total 24 Claims	24 -20 =	4	X \$28.00	\$ 72.00
Independent Claims	3 -3 =	-0-	X \$74.00	\$ -0-

Multiple dependent claims(s) (if applicable)	+ \$230.00	\$ -0-
<b>TOTAL OF ABOVE CALCULATIONS</b>		<b>= \$ 932.00</b>

Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement  
 must also be filed. (Note 37 CFR 1.9, 1.27, 1.28). \$ -0-

**SUBTOTAL** = \$ 932.00

Processing fee of \$130.00 for furnishing the English translation later the ☐ 20 ☐ 30  
 months from the earliest claimed priority date (37 CFR 1.492(f)). + \$ -0-

**TOTAL NATIONAL FEE** = \$ 932.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be  
 accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property + \$ -0-

**TOTAL FEES ENCLOSED** = \$ 932.00

Amount to be:	
refunded	\$
charged	\$

a. ☒ A check in the amount of \$\*\*932.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees.  
 A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any  
 overpayment to Deposit Account No. 19-0450. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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*Edwin D. Schindler*  
 SIGNATURE

Edwin D. Schindler

NAME

31,459

REGISTRATION NUMBER

09/743206  
528 Rec'd PCT/PTO 04 JAN 2001

BET  
5.17.01  
#41 PRE  
Amor  
PATENT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: DAWOOD PARKER/D. HARRISON ART UNIT:

SERIAL NO.: 09/

EXAMINER:

FILED:

P.C.T. APPLICATION NO.: PCT/GB99/02127

TITLE: NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES

PRELIMINARY AMENDMENT

Hon. Commissioner for Patents  
United States Patent and Trademark Office  
Box PCT  
Washington, D. C. 20231

Dear Sir:

Prior to an examination on the merits of the above-identified patent application, please amend the above-identified application as follows:

IN THE SPECIFICATION

Please amend the Specification (which includes an Article 19 Amendment as part of the IPEA/EP International

"Express Mail" mailing label number EF 310251681 US  
Date of Deposit January 4, 2001

I hereby certify that this paper is being deposited with the U.S. Postal Service "Express Mail - Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to: Hon. Commissioner for Patents, United States Patent and Trademark Office, Washington, D. C. 20231.

  
Edwin D. Schindler, Reg. No. 31,459

January 4, 2001  
Date

Preliminary Examination Report) as follows:

Page 1, immediately beneath the Title of the Invention, insert the following headings:

--BACKGROUND OF THE INVENTION--; and,

--Technical Field of the Invention--; and,

between lines 12-14 (as numbered along the left-hand margin of the page, which might not be the same as the actual number of lines on the page), insert the following heading:

--Description of the Prior Art--.

Page 5 ("Amended Sheet"), between lines 24-26, insert the following heading:

--SUMMARY OF THE INVENTION--.

Page 7, between lines 25-27, insert the following heading:

--BRIEF DESCRIPTION OF THE DRAWING FIGURES, EXPERIMENTAL DATA AND PREFERRED EMBODIMENTS--

IN THE CLAIMS

Please cancel Claims 1-32, as examined during the P.C.T. international phase (which were the subject of the Chapter II International Preliminary Examination Report and attached thereto), and substitute therefor the following claims:

--33. An apparatus for a non-invasive measurement of at least one analyte in blood in a body part of a patient, comprising:

a light transmitter having a plurality of transmitting fibers positioned for transmitting light to the body part of the patient;

a light detector having a plurality of light detector fibers for detecting light transmitted through, or reflected from, the body part of the patient; and,

means for utilizing a non-pulsatile element of the blood in the body part of the patient for determining a measurement of at least one analyte in the blood.

A3

34. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, further comprising means for utilizing a pulsatile element of the blood in the body part of the patient for determining the measurement of at least one analyte in the blood.

35. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, further comprising a plurality of closely associated transmitters and generators for providing an "average-evened out" signal to be produced for representing the measurement of at least one analyte in the blood.

36. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, further

comprising means for measuring blood glucose level.

37. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, further comprising means for measuring blood oxygen saturation (SO<sub>2</sub>).

38. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 37, wherein said means for measuring blood oxygen saturation (SO<sub>2</sub>) includes calculation means using the equation:

$$SO_2 = 100 \cdot (OXI + 0.43) / 1.5,$$

wherein,

OXI is the oxygenation index of the blood of the patient and is defined by the equation:

$$OXI = [(e - d) / 11.7 - (d - c) / 11.6] \cdot 100 / HbI,$$

wherein,

HbI is the hemoglobin index of the blood of the patient and is defined by the equation:

$$HbI = [(b-a) / 27.1 + (c-b) / 21.4 + (c-e) / 23.3 + (c-f) / 13.6] \cdot 100$$

and wherein,

a = absorption value at 500.9 nm wavelength of light;

b = absorption value at 528.1 nm wavelength of light;

c = absorption value at 549.5 nm wavelength of light;

d = absorption value at 561.1 nm wavelength of light;

e = absorption value at 572.7 nm wavelength of light;

and,

f = absorption value at 586.3 nm wavelength of light.

39. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, further comprising means for measuring hemoglobin index (HbI).

40. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 39, wherein said means for measuring the hemoglobin index (HbI) includes calculation means using the equation:

$$\text{HbI} = [(b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6] \cdot 100$$

wherein,

a = absorption value at 500.9 nm wavelength of light;

b = absorption value at 528.1 nm wavelength of light;

c = absorption value at 549.5 nm wavelength of light;

d = absorption value at 561.1 nm wavelength of light;

e = absorption value at 572.7 nm wavelength of light;

and,

f = absorption value at 586.3 nm wavelength of light.

41. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, further comprising means for measuring temperature of the blood of the patient.

42. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, wherein said apparatus includes means for measuring at least two analytes in the blood of the patient, said at least two analytes being selected from blood glucose level, blood

oxygen saturation (SO<sub>2</sub>), hemoglobin index (HbI) and temperature of the blood of the patient.

43. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 42, wherein said wherein said means for measuring at least two analytes in the blood of the patient is a computer program.

44. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 43, wherein said computer program conducts a multiple linear regression analysis on spectral data collected by said plurality of light detector fibers.

45. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 42, wherein said apparatus includes means for measuring each of blood glucose level, blood oxygen saturation (SO<sub>2</sub>), hemoglobin index (HbI) and temperature of the blood of the patient.

46. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, wherein said apparatus includes a greater number of said transmitting fibers than said light detector fibers.

47. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, wherein said light detector includes from 6 through 18 of said light detector fibers.



49. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, wherein said light detector fibers and said transmitting fibers each have diameters of from 200 to 300 microns.

50. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, wherein said light detector fibers are positioned for detecting transmitted light rather than reflected light.

51. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 33, wherein said plurality of transmitting fibers use a wavelight of light of from 500 to 1,100 nm.

52. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 51, wherein said plurality of transmitting fibers use a wavelight of light of from 800 to 1,100 nm.

53. The apparatus for a non-invasive measurement of at least one analyte in blood according to Claim 51, wherein members of said plurality of transmitting fibers used transmit light having each of the wavelengths of 500.9 nm, 528.1

$$\begin{aligned} & \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \\ & \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \left( \frac{1}{\sqrt{2}} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) \end{aligned}$$

AB

placing against a body part of a patient an apparatus for a non-invasive measurement of at least one analyte in blood in a body part of a patient, said apparatus comprising:

a light detector having a plurality of light detector fibers for detecting light transmitted through, or reflected from, the body part of the patient;

means for measuring blood oxygen saturation  
(SO<sub>2</sub>), said means for measuring blood oxygen

saturation (SO<sub>2</sub>) including calculation means using the equation:

$$SO_2 = 100 \cdot (OXI + 0.43) / 1.5,$$

wherein,

OXI is the oxygenation index of the blood of the patient and is defined by the equation:

$$OXI = [(e - d) / 11.7 - (d - c) / 11.6] \cdot 100 / HbI,$$

wherein,

HbI is the hemoglobin index of the blood of the patient and is defined by the equation:

$$HbI = [(b-a) / 27.1 + (c-b) / 21.4 + (c-e) / 23.3 + (c-f) / 13.6] \cdot 100$$

and wherein,

a = absorption value at 500.9 nm wavelength of light;

b = absorption value at 528.1 nm wavelength of light;

c = absorption value at 549.5 nm wavelength of light;

d = absorption value at 561.1 nm wavelength of light;

e = absorption value at 572.7 nm wavelength of light;

and,

f = absorption value at 586.3 nm wavelength of light;

and,

utilizing said light detector of said apparatus for measuring light transmitted through, or reflected from the body part of the patient.

56. A computer program for measuring one or more of the hemoglobin index, the oxygenation index or the blood oxygen saturation level in blood of a patient, comprising:

a computer readable medium having computer program code means on said computer readable medium, said computer program code means calculating one or more of the following equations:

HbI is the hemoglobin index of the blood of the patient and is defined by the equation:

$$\text{HbI} = [(b-a)/27.1 + (c-b)/21.4 + (e-d)/23.3 + (f-g)/13.6] * 100$$

wherein,

a = absorption value at 500.9 nm wavelength of light;

b = absorption value at 528.1 nm wavelength of light;

c = absorption value at 549.5 nm wavelength of light;

d = absorption value at 561.1 nm wavelength of light;

e = absorption value at 572.7 nm wavelength of light;

and,

f = absorption value at 586.3 nm wavelength of light;

OXI is the oxygenation index of the blood of the patient and is defined by the equation:

$$\text{OXI} = [(e - d)/11.7 - (d - c)/11.6] * 100/\text{HbI}; \text{ and,}$$

SO<sub>2</sub> is the blood oxygen saturation of the blood of the patient and is defined by the equation:

$$\text{SO}_2 = 100 * (\text{OXI} + 0.43)/1.5.--$$

#### REMARKS

Prior to an examination on the merits of the above-identified patent application, please enter the foregoing preliminary amendments.

Claims 33-56, as entered herein, are pending in the above-identified patent application. All prior claims, entered during the P.C.T. international phase, have been cancelled. Claims 33, 55 and 56 are the independent claims pending in this application.

The Specification has also been provided with standard U.S. sectional headings.

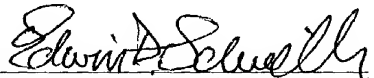
The Examiner is reminded that Pages 5 and 5a, as amended, are attached to the International Preliminary Examination Report, prepared by the European Patent Office, a copy of which is being concurrently filed.

The application is now in condition for a full examination on the merits.

Accordingly, an early examination on the merits and allowance are, therefore, respectfully requested and earnestly solicited.

Respectfully submitted,

DAWOOD PARKER/D. HARRISON

By   
Edwin D. Schindler  
Attorney for Applicants  
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January 4, 2001

QAD  
A1NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES

This invention relates to a novel monitor, particularly a monitor for the non-invasive measurement of glucose in eg diabetics and a method for determining glucose levels.

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Diabetes mellitus (abbreviated to diabetes) is the name for a group of chronic or lifelong diseases that affect the way the body uses food to make energy necessary for life. Primarily, diabetes is a disruption of carbohydrate (sugar and starch) metabolism and also affects fats and proteins. In people who have diabetes the glucose levels vary considerably being as high as 40 mmol/l and as low as 2 mmol/l. Blood glucose levels in people without diabetes vary very little, staying between 3 and 7 mmol/l. These levels follow the typical patterns shown in Figure 1a.

DESCRIPTION OF THE PRIOR ART**Hyperglycaemia (high blood glucose)**

Both insulin dependant diabetes (IDDM) and non-insulin dependant diabetes (NIDDM) are associated with serious tissue complications which characteristically develop after 10-20 years duration of diabetes. Diabetic eye disease, retinopathy, is the commonest cause of blindness in western countries in people under the age of 65 years. Diabetic renal disease, nephropathy, is an important cause of kidney failure in the community. Diabetic neuropathy affects the peripheral nerves causing impaired sensation and leg ulcers, and damage to the autonomic nervous system causes postural hypertension (low blood pressure on standing) and diarrhoea. Atherosclerosis is 2-4 times as high in diabetic as non-diabetic people and manifest as an increased frequency of myocardial infarction (heart attacks), cerebrovascular disease (strokes) and the peripheral vascular disease (causing reduced circulation to the limbs and the risk of gangrene and amputation).

For many years it has been something of an article of faith in clinical diabetes that the cause of the complications is exposure of the tissues over many years to the higher than normal blood glucose levels which have been usual in most treated diabetic patients. Conclusive proof of this theory has only recently become

available; the landmark Diabetes Control and Complications Trial (DCCT) in North America was announced in 1993 and showed that IDDM patients randomly assigned to an intensive and optimised insulin treatment programme designed to produce near-normal blood glucose levels had significantly less retinopathy, kidney disease and neuropathy over a 9-year period than patients assigned to ordinary treatment (ie poor control).

The DCCT has been a major stimulus to physicians around the world to renew efforts to improve control in diabetic patients, and to develop improved methods of obtaining good control and of monitoring these patients.

#### **Hypoglycaemia (low blood glucose)**

An important additional finding in the DCCT was that the frequency of hypoglycaemia was three-fold higher in the well-controlled patients than those with ordinary control. This confirms the long-standing appreciation by physicians that hypoglycaemia is extremely frequent in IDDM, and especially so in those that are well controlled. There are many reasons for this including mistiming of insulin injections and food, erratic absorption of insulin, and impaired secretion in some diabetic patients of the so-called counter regulatory hormones such as adrenaline and glucagon that oppose the action of insulin.

About one third of IDDM patients have no warning symptoms of hypoglycaemia (eg sweating, nausea, blurred vision, palpitations) and they rely on intermittent self-monitoring of blood glucose to detect dangerously low glucose levels. The consequences of hypoglycaemia include impaired cognition and consciousness, and eventually coma.

Since the late 1970's, an increasing number of diabetic patients, mostly IDDM, have been measuring their own blood glucose concentrations using finger-prick capillary blood samples. Self blood glucose monitoring (SBGM) is used by diabetics in the home to detect hypoglycaemia or hyperglycaemia and take corrective action such as

taking extra food to raise the blood glucose or extra insulin to lower the blood glucose. The measurements, which are made using a low-cost, hand-held blood glucose monitor (BGM), also allow the physician to adjust the insulin dosage at appropriate times so as to maintain near normoglycaemia.

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BGMs use either reflectance photometry or an electrochemical method to measure the glucose concentration. Reflectance photometry measures the amount of light reflected from the reagent-impregnated test strip that has reacted with a drop of blood. The operator pricks the finger of the patient or earlobe with a sterile lancet or  
10 uses anticoagulated whole blood collected in heparin and then places the blood on the test strip. The operator must place the blood onto the test strip at the time the monitor begins its timing sequence. This step is critical because under-timing (under-incubation) or over-timing (over-incubation) of the reaction may cause inaccurate measurements. At the audible signal, the operator wipes or blots the  
15 excess blood off the outside of the test strip. The operator then inserts the strip into the monitor for measurement.

In the electrochemical method a disposable single-use enzyme electrode test strip is used. When the test specimen is placed onto the test strip, an enzymatic reaction  
20 occurs that results in a current through the strip. The current is directly proportional to the concentration of glucose in the specimen.

The main disadvantages of SBGM systems are poor patient acceptance because the technique is painful, only intermittent assessment of diabetic control is possible and  
25 readings during the night or when the patient is otherwise occupied such as during driving are not possible. It is estimated that less than half of the IDDM patients in the US perform SBGM.

Further, glucose values obtained with BGMs may not agree with clinical laboratory  
30 results. Routine laboratory measurements of glucose are performed on either serum



or plasma venous blood specimens that correspond with glucose concentrations measured on whole blood glucose analysers.

Whole blood glucose values are lower than those obtained from either serum or plasma. Although glucose is not a static component in human blood, changes in blood glucose concentration following food intake in normal and hyperglycaemic conditions are reasonably predictable. Similarly, the variation in glucose concentration as blood passes from arteries or capillaries to veins has also been documented. Therefore, over time, repeated measurement of blood glucose from the same patient may diverge widely. Also, blood obtained simultaneously by finger stick and venipuncture may not have the same glucose concentration. (Venous blood may contain 1 mmol/l less glucose than capillary blood if the same samples are obtained within 1-2 hours after carbohydrate intake).

Furthermore, the haematocrit of the patient (the volume of cells, mostly erythrocytes, expressed as a percentage of the volume of whole blood in a sample) influences glucose values, and whole blood glucose measurements must be corrected for this. Unfortunately, because BGMs cannot automatically correct for the haematocrit of the patient, an error of 5-15% may be introduced.

There is widespread agreement that for self-monitoring in the home the reluctant acceptance of the current finger-stick method is the main reason why the development of a non-invasive measurement technique has such high priority.

A non-invasive measurement device is known from US Patent No 5,553,613. US '613 describes a technique which uses the pulsatile component of the light intensity transmitted through the finger, from which to derive the glucose concentration non-invasively. It does this by using the wavelengths 805nm, 925nm, 970nm and the range 1000-1100nm. The measurements were made by transmission, ie light was passed through the finger. However, as mentioned above, US '613 specifically relies upon the pulsatile component of the light transmitted through the patient. Such a

## ART 34 AMDT

pulsatile technique has clear disadvantages in that the pulsatile component of the light signal, whether transmitted or reflected, is less than 2% of the total signal. Thus, prior art devices which use only the pulsatile component are much less sensitive and much more vulnerable to patient movement which can cause interference which is in the order of a few hundred times the relevant signal.

Moreover, the pulsatile signal identifies arterial blood specifically. Whilst this is advantageous when considering the pulmonary circulation of a patient, it provides no information on the patient's systemic circulation which is important for glucose determination. Further, pulsatile techniques are limited to use on body extremities, eg finger, ear lobe or the ball of the foot in babies or neo-nates.

International Patent Application No. WO 97/27800 discloses a device for the non-invasive measurement of blood analytes using light transmitted through or reflected from a body part.

However, the invention disclosed in the prior art also suffers from the disadvantage that, *inter alia*, only the pulsatile element of the transmitted/reflected signal is exploited.

US Patent No. 5,755,226 describes an apparatus for the non-invasive measurement of blood glucose levels. Furthermore, the disclosed invention does not describe the utilisation of the non-pulsatile element of a patient's blood in the determination of blood analytes.

25 Summary of the invention

The present invention overcomes or mitigates the disadvantages of the prior art by using a plurality of closely associated transmitters and generators which allows an "average" evened out signal to be produced and is capable of utilising the non-pulsatile element of the patient's blood flow. In addition, a further advantage of the invention is that it allows the measurement of oxygen saturation ( $SO_2$ ).

According to the invention we provide a device for the non-invasive measurement of one or more analytes in blood in a patient's body part which comprises a light transmitter comprising a plurality of transmitting fibres positioned to transmit light to the body part and a light detector comprising a plurality of light detector fibres positioned to detect light transmitted through or reflected from the body part.

10 A preferred embodiment of the invention is one wherein the non-pulsatile element of the patient's blood is utilised. Thus, according to a further feature of the invention we provide a device for the non-invasive measurement of one or more analytes in blood in a patient's body part as herein before described which is adapted to measure the non-pulsatile element of a patient's blood. In a further preferred embodiment the

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device measures the pulsatile and non-pulsatile elements of a patient's blood. The device may be so adapted by being provided with a plurality of closely associated transmitters and generators which allows an "average" evened out signal to be produced.

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Although various analytes may be measured, the detector of the invention is especially useful in measuring blood glucose level. We especially provide a device for the non-invasive measurement of one or more analytes in blood in a patient's body part as herein before described which is adapted to measure blood glucose levels.

10

The device may be capable of measuring other parameters either separately or in addition to blood glucose. An especially advantageous feature is the device may be adapted to measure blood oxygen saturation (SO<sub>2</sub>).

15 As a further preferred embodiment we provide a device which is adapted to measure the haemoglobin index (HbI) and/or temperature of a patient's blood.

The device may be adapted for use, with any body part although it is preferable that it can be a finger or thumb.

20

The number of transmitter fibres may vary although we have found that 18 transmitter fibres works well. The number of detector fibres may be the same or different to the number of transmitter fibres, but may vary and we have found that 12 detector fibres works well. The diameter of the detector and the transmitter fibres may be the same or different and may vary, a diameter of 250µm is preferred.

25

The detector fibres are preferably positioned to detect reflected light rather than transmitted light.

30 The wavelength used in the transmitter fibres will generally be from 500 to 1100nm. However, it is a further feature of the invention to provide a detector as hereinbefore

described which also measures haemoglobin index (HbI) and/or oxygen saturation (SO<sub>2</sub>) of blood. For such measurement, specific wavelengths are used, namely 500.9nm, 528.1nm, 549.5nm, 561.1nm, 572.7nm and 586.3nm. The preferred wavelengths for measuring blood glucose are from 800nm to 1100nm.

5

According to a further feature of the invention we provide a method of measuring blood glucose levels which comprises placing a non-invasive measuring device as hereinbefore described against a body part of a patient and using the detector to measure the light transmitted through or reflected from the body part.

10

In a yet further feature of the invention we provide a device according to as herein before described programmed so as to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation. Clearly, since blood oxygen saturation is dependent upon both the haemoglobin index and the oxygen

15 index, the computer is programmed so as to calculate these equations first if blood oxygen saturation is to be calculated.

20

We also provide a computer programme product comprising a computer readable medium having thereon computer programme code means, when said programme is loaded, to make the computer execute a procedure to calculate one or more of the haemoglobin index, the oxygen index and the "whole blood" oxygen saturation as herein before described.

25

The invention will now be illustrated but in no way limited by reference to the following example and drawings in which;



Figure 1 is a plot of the predicted glucose values against the measured glucose values; and

Figure 1a is a graph comparing normal blood glucose levels with those of a

30 diabetic.

## Example 1

### Glucose measurement

- In vivo* measurements using the MCPD spectrophotometer were carried out at 10 min intervals on the fingertips of 8 volunteers during the course of glucose tolerance tests and the results compared with those measured using a conventional blood glucose monitor. In addition, parallel measurements of local blood flow (laser Doppler flux) and temperature were made.
- The analysis which is presented here uses the same wavelength range used in the previous glucose studies carried out namely: 805nm, 925nm, 970nm and the broadband average 1000-1100nm, but additionally wavelengths sampled at regular intervals in the entire range 800nm to 1100nm. Intervals of 1.96nm worked well.
- Earlier work demonstrated that the glucose-dependent signal emanates from haemoglobin. Furthermore, although the 805nm wavelength could be used to compensate for small changes in haemoglobin concentration large changes continued to interfere with the sensitivity for glucose. It was furthermore recognised that changes in haemoglobin oxygenation would cause absorption changes from 800nm to 1100nm. As in all physiological measurements carried out in the peripheral circulation, temperature is also likely to be a controlling parameter. In the novel analysis carried out on the intensity spectra in the experiments carried out here, the three parameters haemoglobin concentration, oxygen saturation and temperature were introduced into the multiple linear regression analysis along with the near infrared parameters previously used.

### Experimental

- 13 glucose tolerance tests (GTTs) were carried out on 8 different volunteers. In one case, 200ml water was given instead of the solution of 75g glucose in 200ml water; a real GTT was subsequently carried out on the same volunteer. In one volunteer five GTTs were carried out on separate occasions. One volunteer had diabetes.

All measurements were carried out with an Otsuka Optronics Photol MCPD-1000 photodiode array lightguide spectrophotometer. The 0.2mm slit was used for the diffraction grating giving a full width at half maximum transmission of 7.2nm, comparable with the glucose monitor. Using the supplied software, the instrument allows access to data points at 1.94nm intervals within the wavelength range 300-1100nm. The range displayed during the glucose experiments was 500-1100nm. In order to mimic the broad bandwidth characteristics of the previous glucose monitor above 1000nm, all measurements were averaged over the range 1000-1100nm.

10 Quartz lightguides were used in conjunction with a 400W quartz-halogen light source.

A lightguide bundle, which consisted of 18 transmitting and 12 receiving fibres each of 250µm diameter, was attached to the fingertip of the subject by means of a laser Doppler probe holder. Recordings of spectra were made at 10 min intervals throughout the test using the MCPD spectrophotometer described above. These recordings were accompanied by parallel measurements of glucose concentrations in blood, obtained by pinprick of a contralateral finger with the aid of a Softelix pro lancet system, using a Boehringer Mannheim Advantage® glucose monitor. The lightguide was removed from the finger after each measurement and new dark and reference spectra recorded before each new measurement. A total of 13 measurements were carried out over a 2 hour period.

Careful selection of integrating time and the intensity of the reference spectrum enabled the simultaneous record of spectra that covered not only the range 800-1100nm, but also the visible range from 500-600nm. This enabled the evaluation of skin haemoglobin saturation (SO<sub>2</sub>) and haemoglobin concentration (HbI) (Harrison DK *et al*, (1993) *Phys Meas* 14: 241-52) from the same spectra as those being analysed for glucose (see below).

A Moor Instruments DRT4 laser Doppler perfusion monitor was used to measure blood flow changes in the adjacent finger. The probe incorporated a thermal sensor, which was used to measure skin temperature (note: also on the adjacent finger) throughout the experiment.

5

#### Derivation of HbI and SO<sub>2</sub>

HbI and SO<sub>2</sub> were derived from the absorption spectra measured from 500.8 to 586.3nm using a computer program VOXYG written for the purpose. The program carried out the following calculations.

10

#### *Haemoglobin Index*

$$\text{HbI} = ((b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6) * 100$$

15

#### *Oxygenation Index*

$$\text{OXI} = (c-d)/11.7 - (d-c)/11.6 * 100 / \text{HbI}$$

#### *Oxygen Saturation*

20

$$\text{SO}_2 = 100 * (\text{OXI} + 0.43) / 1.5$$

where a = absorption value at 500.9nm

b = absorption value at 528.1nm

25

c = absorption value at 549.5nm

d = absorption value at 561.1nm

e = absorption value at 572.7nm

f = absorption value at 586.3nm

#### 30 MULTIPLE LINEAR REGRESSION ANALYSIS



A data file A was created containing the full absorption spectral data (800-1100nm in 1.96nm steps) from all 12 GTTs in the series. The absorption values in the file are defined in "absorption units" referred to here as ABUs. The other data contained in the file were time, experiment identification, glucose concentration (invasive), HbI, SO<sub>2</sub>, temperature, and laser Doppler flux.

A number of secondary files were created whereby a sequence of "normalisations" of the data were performed:

- 10 • B - ABU data of A was normalised by subtraction of the absorption of the values at 802nm (ie  $ABU_A - ABU_{802}$ ). This is similar to the way in which previous data was treated.
- C - ABU data of B was further normalised by division by the HbI value (ie  $ABU_B/HbI$ ). This was designed to take into account of the results of the *in vitro* experiments which showed that normalisation at, then, 805nm did not fully compensate for changes in haemoglobin concentration.
- 15 • D - ABU data of C was further normalised by division by the SO<sub>2</sub> value (ie  $ABU_C/SO_2$ ) to take into account the influence of changes in the relative concentrations of oxygenated haemoglobin (HbO<sub>2</sub>) and deoxygenated haemoglobin (Hb) on the infrared spectrum.
- 20 • E - SBU data of D was yet further normalised by subtraction of the value at the assumed water peak (ie  $ABU_D - ABU_{949}$ ) in an attempt to take into account changes in water content.
- 25 The types and orders of normalisations may vary, and the above are examples.

The above files were then subjected to multiple linear regression, analysis using SPSS for Windows 6.1.2. All of the wavelengths available in the above data files, ie 800nm to 1100nm in 1.96nm steps were entered as independent variables. The results of the multiple wavelength regressions are given below. The regressions



## CLAIMS

1. A device for the non-invasive measurement of one or more analytes in blood in a patient's body part which comprises a light transmitter comprising a plurality of transmitting fibres positioned to transmit light to the body part and a light detector comprising a plurality of light detector fibres position to detect light transmitted through or reflected from the body part characterised in that it is adapted to utilise the non-pulsatile element of a patient's blood.
2. A device according to Claim 1 characterised in that it is adapted to utilise the non-pulsatile and the pulsatile elements of a patient's blood.
3. A device according to Claim 2 characterised in that it is so adapted by being provided with a plurality of closely associated transmitters and generators which allow an "average" evened out signal to be produced.
4. A device according to Claim 1 characterised in that it is adapted to measure blood glucose levels.
5. A device according to Claim 1 characterised in that it is adapted to measure blood oxygen saturation ( $SO_2$ ).
6. A device according to Claim 1 characterised in that it is adapted to measure the haemoglobin index (HbI).
7. A device according to Claim 1 characterised in that it is adapted to measure the temperature of a patient's blood.
8. A device according to Claim 1 characterised in that it is adapted to measure two or more analytes in blood, which analytes are selected from blood glucose levels,

blood oxygen saturation (SO<sub>2</sub>), the haemoglobin index (HbI) and the temperature of a patient's blood.

9. A device according to Claim 8 characterised in that it is adapted to measure  
5 blood glucose levels, blood oxygen saturation (SO<sub>2</sub>), the haemoglobin index (HbI) and the temperature of a patient's blood
10. A device according to Claim 1 characterised in that it is adapted to measure of one or more analytes in blood in a patient's finger or thumb.
- 10 11. A device according to Claim 1 characterised in that it is provided with a greater number of transmitter fibres than detector fibres.
12. A device according to Claim 1 characterised in that it is provided with from 6  
15 to 18 detector fibres.
13. A device according to Claim 12 characterised in that it is provided with 12 detector fibres.
- 20 14. A device according to Claim 1 characterised in that diameter of the fibres is from 200 - 300µm.
15. A device according to Claim 1 characterised in that the detector fibres are positioned to detect transmitted light rather than reflected light.
- 25 16. A device according to Claim 1 characterised in that the wavelength used in the transmitter fibres is from 500 to 1100nm.
17. A device according to Claim 16 characterised in that the wavelength used in  
30 the transmitter fibres is from 800 to 1100nm.

18. A device according to Claim 17 characterised in that the wavelength used in the transmitter fibres is 805nm, 925nm, 970nm and the broadband average 1000-1100nm.
- 5 19. A device according to Claim 17 characterised in that the wavelengths are sampled at regular intervals of 1.96nm in the entire range 800nm to 1100nm.
20. A device according to Claim 16 characterised in that the wavelength used in the transmitter fibres is from 500 to 600nm.
- 10 21. A device according to Claim 16 characterised in that the wavelength used in the transmitter fibres is 500.9nm, 528.1nm, 549.5nm, 561.1nm, 572.7nm and 586.3nm.
- 15 22. A device according to Claim 16 characterised in that the wavelength used in the transmitter fibres is 500.9nm, 528.1nm, 549.5nm, 561.1nm, 572.7nm and 586.3nm; and from 800nm to 1100nm.
- 20 23. A method of measuring blood glucose levels which comprises placing a non-invasive measuring device as herein before described against a body part of a patient and using the detector to measure the light transmitted through or reflected from the body part characterised in that the non-pulsatile element is used.
24. A method according to Claim 23 characterised in that the non-pulsatile and
- 25 pulsatile element is used.
25. A device according to Claim 1 programmed so as to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation.
- 30 26. A device according to Claim 25 programmed so as to conduct a multiple linear regression analysis on spectral data collected by the detectors.

27. A device according to Claim 25 wherein the Haemoglobin Index is calculated using the equation:

5 
$$\text{HbI} = ((b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6) * 100$$

where

a = absorption value at 500.9nm  
b = absorption value at 528.1nm  
c = absorption value at 549.5nm  
10 e = absorption value at 572.7nm  
f = absorption value at 586.3nm.

28. A device according to Claim 30 wherein the Oxygenation Index is calculated using the equation:

15 
$$\text{OXI} = (e - d) / 11.7 - (d - c) / 11.6 * 100 / \text{HbI}$$

where

c = absorption value at 549.5nm  
d = absorption value at 561.1nm  
20 e = absorption value at 572.7nm.

29. A device according to Claim 25 wherein the Oxygen Saturation ( $\text{SO}_2$ ) is calculated using the equation:

25 
$$\text{SO}_2 = 100 * (\text{OXI} + 0.43) / 1.5$$

30. A method of measuring blood oxygen saturation which comprises placing a non-invasive measuring device as herein before described against a body part of a patient and using the detector to measure the light transmitted through or reflected from the body part using a device according to Claim 29.

31. A computer programme product comprising a computer readable medium having thereon computer programme code means, when said programme is loaded, to make the computer execute a procedure to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation characterised in that the computer programme code means will make the computer execute a procedure to calculate one or more of :

$$\text{HbI} = ((b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6) * 100;$$

$$\text{OXI} = (e-d)/11.7 - (d-c)/11.6 * 100/\text{HbI}; \text{ and}$$

$$\text{SO}_2 = 100 * (\text{OXI} + 0.43) / 1.5$$

where

a = absorption value at 500.9nm

b = absorption value at 528.1nm

c = absorption value at 549.5nm

d = absorption value at 561.1nm

e = absorption value at 572.7nm

f = absorption value at 586.3nm

32. A device substantially as described with reference to the accompanying examples and drawings.

25

P36002WU.3claims

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International Bureau

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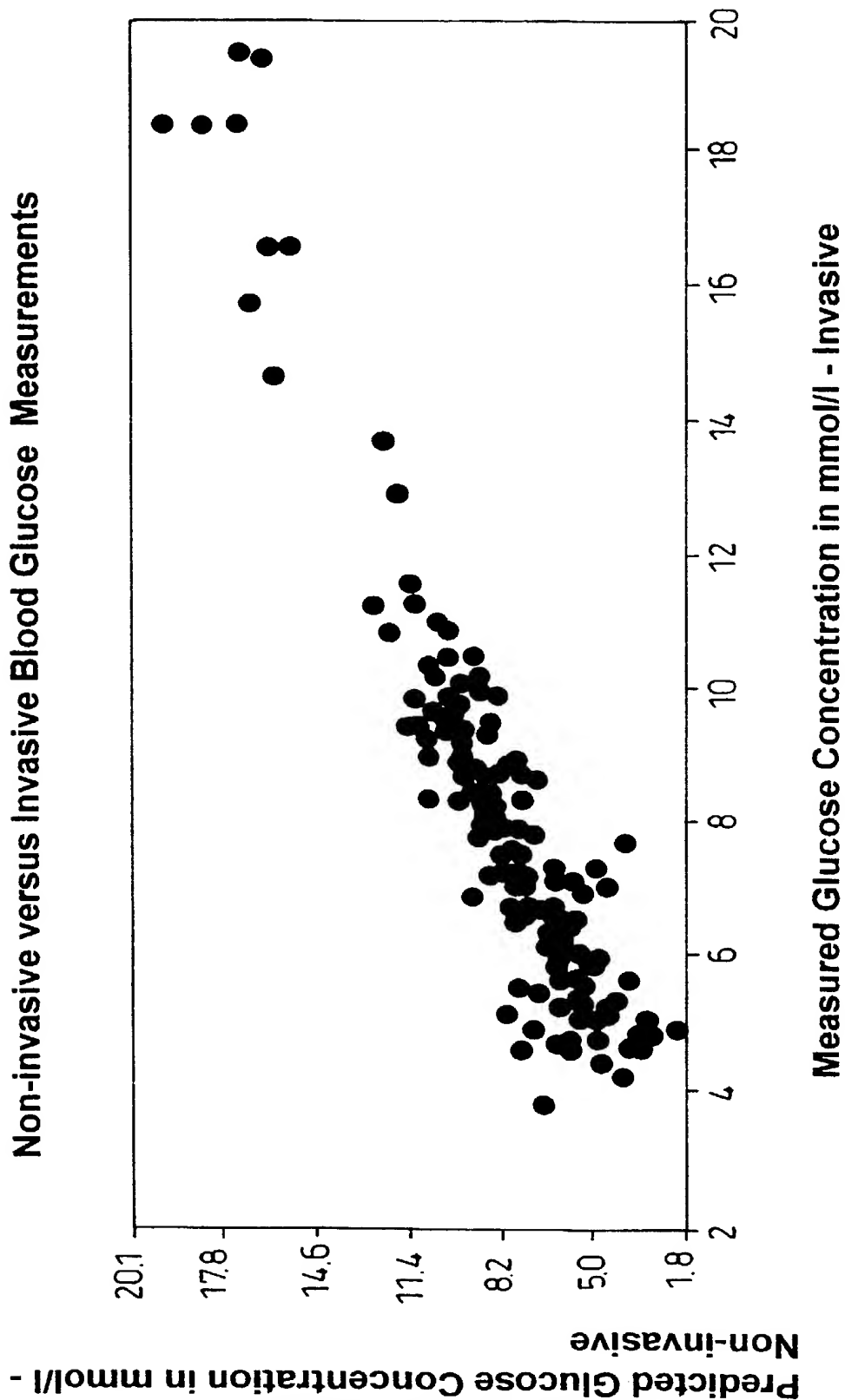


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(54) Title: NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES  (57) Abstract  <p>There is described a device for the non-invasive measurement of one or more analytes in blood in a patient's body part which comprises a light transmitter comprising a plurality of transmitting fibres positioned to transmit light to the body part and a light detector comprising a plurality of light detector fibres position to detect light transmitted through or reflected from the body part. The device especially utilises the non-pulsatile element of a patient's blood. There is also described a method of measuring blood glucose levels and a device programmed so as to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation.</p>			

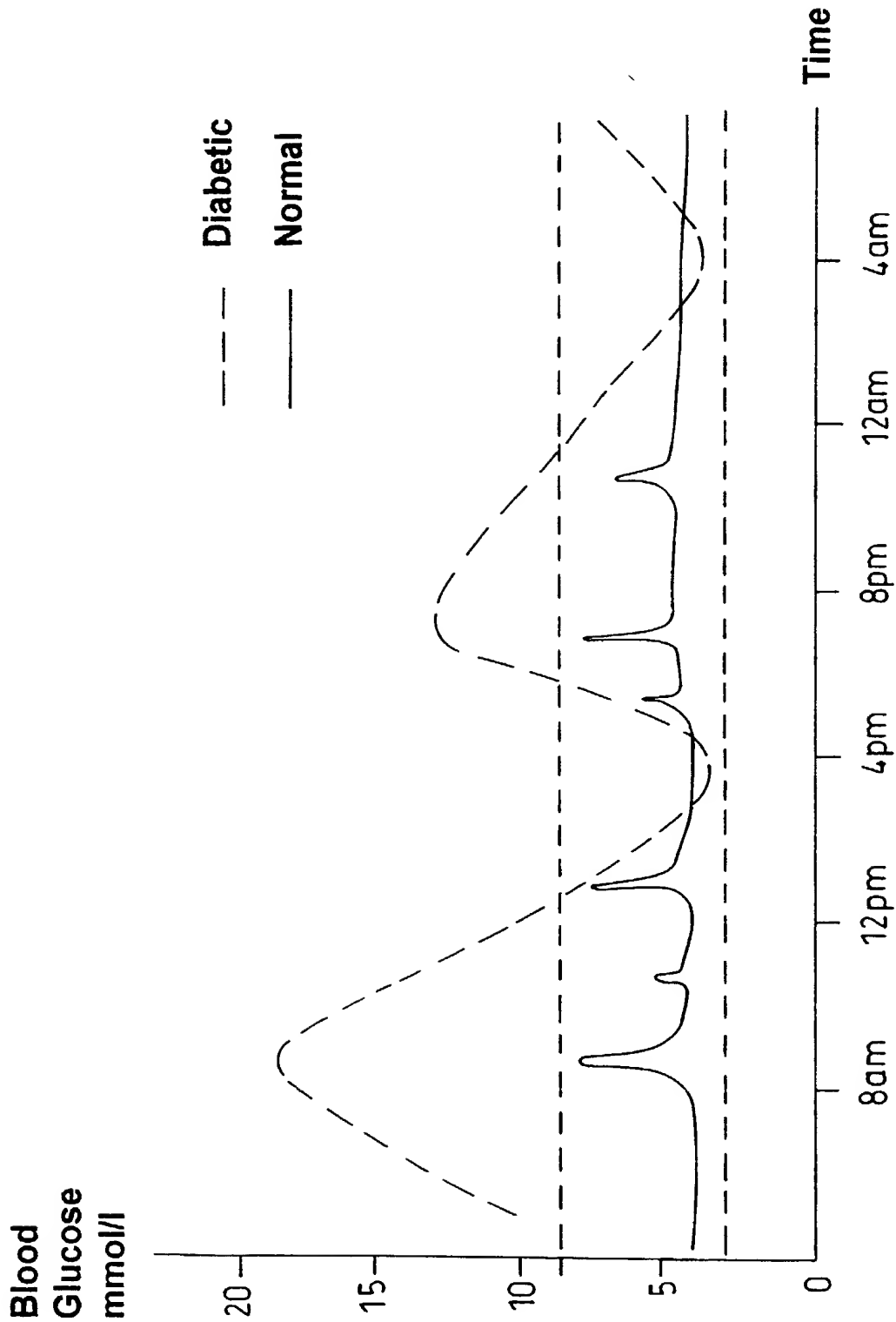


1/2



*Fig. 1*

2/2



An example of blood glucose levels during the day

*Fig. 1a*

## Declaration and Power of Attorney For Patent Application

### English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on July 2, 1999 as

P.C.T.-Application Serial No. PCT/GB99/02127

and was amended on \_\_\_\_\_  
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
9814464.5	United Kingdom	04 July 1998	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Day/Month/Year Filed)		
9824899.0	United Kingdom	13 November 1998	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Day/Month/Year Filed)		
9825243.0	United Kingdom	19 November 1998	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)

(Filing Date)

(Status)  
(patented, pending, abandoned)

(Application Serial No.)

(Filing Date)

(Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

①

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Full name of second joint inventor, if any	<u>David Keith Harrison</u>	
Second inventor's signature	<u><i>D K Harrison</i></u>	Date
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TO

0016314745374 P.02

Applicants: Dawood Parker/David Keith Harrison  
Serial No.: 09/743,206  
Filed:  
For: NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS  
(37 CFR 1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

☐ the owner of the small business concern identified below:

☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN Whitland Research Limited  
ADDRESS OF CONCERN Whitland Abbey, Whitland  
Carms SA34 0LG, United Kingdom

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled

NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES  
by inventors Dawood Parker/David Keith Harrison  
described in

☐ the specification filed herewith  
☒ P.C.T. Application No. PCT/GB99/02127,  
filed July 4, 1998  
☐ patent no. \_\_\_\_\_ issued \_\_\_\_\_

01-MAR-2001 15:43 FROM HARRISON GODDARD FOOTE TO 0016314745374 P.03

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below and now rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 CFR 1.9(d) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e). NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

FULL NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN  
☐ NON-PROFIT ORGANIZATION

FULL NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN  
☐ NON-PROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in the loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. 1.28(b))

I hereby declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING \_\_\_\_\_

DAWOOD PARKER

TITLE OF PERSON OTHER THAN OWNER Director of Research

ADDRESS OF PERSON SIGNING Whitland Research Limited.

Whitland Abbey, Whitland, Carmarthenshire, SA34 0LG, UK.

SIGNATURE \_\_\_\_\_

DATE 1 MARCH 01

(Page 2 of 2 Pages)